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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/859,439	05/18/2001	Indra Prakash	2047.154	3715

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EXAMINER	
ZUCKER, PAUL A	

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 11/17/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/859,439	PRAKASH, INDRA	
	Examiner	Art Unit	
	Paul A. Zucker	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,14 and 16-20* is/are rejected.

7)☒ Claim(s) *10-13 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Current Status

1. This action is responsive to Applicants' amendment of 5 September 2003 in Paper No 15.
2. Receipt and entry of Applicants' amendment is acknowledged.
3. Claims 1-20 are pending.
4. The rejections under 35 USC § 112, second paragraph, set forth in paragraph 6 of the previous Office Action in Paper No 14 is withdrawn in response to Applicants' amendment.

Outstanding Rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1, 2, 4-9, 14 and 16-20 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Burger et al (Chemmiker Zeitlung 1990, 114(7-8), pages 249-251) and further in view of Claude et al (US 5,510,508 04-1996).

Instantly claimed is a process for the synthesis of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl-L-phenylalanine-1-methyl ester (neotame) via: a) the formation of an oxazolidinone from N-[N-(3,3-dimethylbutyl)-L-α-aspartic acid from a carbonyl compound or its equivalent, followed by b) reacting the oxazolidinone with phenylalanine methyl ester to yield neotame.

Burger teaches (Page 250, left column, lines 17-34) the synthesis of oxazolidinones of general structure 3 (Page 249, upper right-hand column) which, with n=1 (compound 3a), corresponds to that derived from aspartic acid. The amino acid (100 mmol) in anhydrous dimethylsulfoxide is vigorously stirred at room temperature and a gaseous stream of hexafluoroacetone is introduced. The introduction of hexafluoroacetone is stopped when its uptake ceases and reflux is noted. Thus while Burger is silent with respect to the reactant ratios it reasonable to assume the instant claimed slight excess (1:1.1-1.4) of hexafluoroacetone is present. Reaction is continued for 2-3 hours to give the crystalline oxazolidinone after work-up. Burger further teaches (Page 250, last 5 lines of left column- first 9 lines of right column) the aminolysis of the oxazolidinones to form dipeptides such as aspartame. The oxazolidinone (20 mmol) in anhydrous ether is slowly added with stirring at room temperature to a solution of phenylalanine methyl ester (24 mmol) in anhydrous ether (corresponding to 1:1.2 ratio of oxazolidinone:phenylalanine) and reaction continued for 24 hr to give a 72% yield of aspartame.

Burger is silent with respect to application of his process to the synthesis of neotame.

Claude, however, teaches (Column 1, lines 1-42) the structure of neotame, an artificial sweeter closely related in structure to aspartame. The closeness of the relationship between these two compounds is underscored by the fact that Claude

further discloses (Column 3, line 63 – column 4, line 40) the synthesis of neotame in one step from aspartame.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The motivation would have been to apply the efficient process disclosed by Berger for the synthesis of aspartame, a commercially important artificial sweetener, to the synthesis of the aspartame derivative, neotame. There would have been a reasonable expectation for success because aspartame contains the same functional core as neotame and would therefore be expected to react with ketones in a similar fashion.

Response to Applicant's Remarks with Regard to This Rejection

6. Applicant presents several arguments to which the Examiner responds below:
    a. Applicants reference arguments already of record and the Examiner, in reply, references his response to those arguments.
    b. Applicants argue that Chinese Patent Application No. 1174844 contains evidence that aldehydes may be successfully used in the synthesis of aspartame in a process analogous to that employed by Burger. The Examiner agrees that such is the case. The Examiner maintains, however, that this has little, if any, probative value with regard to the patentability of the instantly claimed process over that taught by Burger since Burger employs ketones and not aldehydes.

c. Applicants further argue that the differences in reactivity of the unsubstituted and neohexyl-substituted starting material with aldehydes supports Applicants' contention that one of ordinary skill in the art would not have had a reasonable expectation of success in applying the process of Burger to the synthesis of Neotame. The Examiner disagrees. The mere fact that Applicants have found that the unsubstituted and neohexyl-substituted starting material behave differently in a different process does not mean that one of ordinary skill in the art would not have had a reasonable expectation of success in the application of the process of Burger to the synthesis of Neotame. Applicants have produced no teaching or evidence that the specific differences in the analogous starting materials would have led one of ordinary skill in the art to expect that the neohexyl-substituted starting material could not be employed in the process of Burger.

d. The Examiner agrees with Applicants' characterization (Amendment, page 10, 1st and 2nd full paragraphs) of the positions of Applicants and the Examiner. The Examiner, however, is not persuaded that one of ordinary skill in the art would not have had a reasonable expectation that an N-alkylated substrate would undergo the process taught by Burger. Applicants have provided no evidence that one of ordinary skill in the art would have expected such substitution to interfere in the process of Burger. Applicants' suggestion that the bulk of the neohexyl group would prevent a reasonable expectation of

success in the reaction with *ketones* is not supported by the evidence of record.

e. The difference in reactivity of the prior art substrate and that of invention with baldheads is too remote from the chemistry instantly involved to have probative value. Applicants admit that the reason that baldheads do not work in the case of the inventive process is not clear. In fact, if steric bulk were the issue, as Applicants suggest, the less substituted aldehydes should work better with the more bulky neohexyl-substituted starting material. This is the reverse of what is found by experiment.

Applicant's arguments filed 5 September 2003 have been fully considered but they are not persuasive for the reasons given above.

New Rejections

Claim Rejections - 35 USC § 112

7. Claim 3 is finally rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the limitation "wherein the ketone is selected from the group consisting of dimethyl acetals of hexafluoroactone, dimethyl acetals of hexachloroactone, diethyl acetals of hexachloroactone, and combinations thereof" in lines 1-4. The dialkyl acetals of ketones are not ketones. It is unclear how a ketone can be selected from a group of acetals. Claim 3 is therefore rendered indefinite.

Conclusion

8. Claims 1-20 are pending. Claims 1-9, 14 and 16-20 are rejected. Claims 10-13 and 15 are objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone

number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

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